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LD TYPING FOR BONE MARROW TRANSPLANTATION.(U)
JUN 77 P J ROMANO N00014-76-C-1173
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OFFICE OF NAVAL RESEARCH

Contract N00014-76-C-1173

Task No. NR 207-067

TECHNICAL REPORT NO. 1

LD Typing for Bone Marrow Transplantation

by

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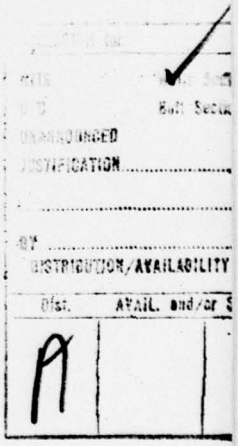
LD TYPING FOR BONE MARROW TRANSPLANTATION

Background

Approximately one year ago, we received a contract to study the role of LD tissue typing in bone marrow transplantation. The primary goal of this work was to identify homozygous typing cells which could be used in various test systems to identify the tissue typing antigens of the fourth locus of the human histocompatibility system.

Bone marrow transplantation will be required for treatment of patients who suffer damage to marrow either through exposure to radiation or to drugs being used in the prophylactic treatment of diseases, such as malaria. Radiation due to tactical atomic warfare could result in thousands of casualties. Current techniques allow for transplantation of bone marrow with identically matched siblings (brothers and sisters), however, the great majority of such patients would require bone marrow transplantation from matched but unrelated individuals in the community. At the present time, tissue typing is inadequate. There are at least four loci which control antigens which are responsible for the rejection or acceptance of tissue grafts. One of these, the LD (HLA-D) locus is the least understood. Separate Navy contracts deal with development of knowledge regarding the specific antigens present at this locus. This contract is directed to the problem of collecting homozygous typing cells which can be used for LD (HLA-D) tissue typing.



Research Design and Plans

During the first year of this contract, we have proposed to study individuals with a high probability of homozygocity at the genetic loci coding for the LD antigen. We had originally suggested that a population of Indians in North Carolina would be studied. This group was identified because of a close breeding and frequent cousin/cousin marriages which

More importantly, some reactions appear to fall outside of the currently known LD types and may provide the basis for identification of a new LD specificity.

d. A panel of over 60 cells have been typed for all known HLA-A, -B, and -C antigens as well as with homozygous cells to establish -D specificities.

Proposal for Continuation of Contract

The initial success and high yield of homozygous typing cells through this contract have provided encouragment that continued pursuit of these efforts should allow us to enlarge the panel not only to provide for greater specificity and identification of currently known LD antigens, but perhaps to provide the basis for expanding our knowledge of LD antigens beyond the current number (7-8) to the anticipated total number of 20-25 specificities which are ascribed to this genetic locus. We would propose to continue work scope essentially as outlined under Accomplishments above (a. through e.) in order to provide a full 100 cell type panel with at least 200 vials of lymphocytes frozen on each of the new LD donors. In addition, we plan to LD type the families described above, as this data should provide much of the genetic information necessary to more clearly define the HL-A D locus. These cells would be made available to the Tissue Typing program of the Naval Medical Research Institute as well as to other ONR contracts dealing with the development of expanded use of HLA tissue typing for transplantation as directed by the Project Officer.

might yield the type of interrelationship leading to homozygous cells. Genetic information on these families was already available through previous testing of this population.

During the first nine months of the contract, considerate effort was made to establish the laboratory in which the typing could be performed. The majority of the equipment is currently available, operative, and the laboratory capable of performing the required tests to identify homozygous LD individuals. Following the initiation of the contract, a local population of individuals who appeared to be homozygous for LD antigens was identified. It was therefore decided to examine this group with preliminary testing to see whether they could yield the type of cells necessary for HLA-D typing. Because of the success of this preliminary venture, much of the problems associated with blood collection at a distance and transport of materials was avoided. The preliminary success has yielded a collection of LD homozygous cells far in excess of that which had been anticipated under the contract.

Data and Results

Accomplishments:

a. Serological testing for HLA-A, B and C loci revealed a population that appeared to be homozygous for these serological determinants. Subsequently, several of these individuals were shown to have cells which were also homozygous for D.

b. Mixed lymphocyte cultures were undertaken between these individuals and members of our HLA-D typed panel as well as other known homozygous typing cells which allowed for identification of the likelihood of homozygocity.

c. Lymphocyte cultures with a panel of known homozygous typing cells enabled us to assign specificities to several of the cells collected.

SUMMARY OF INVENTORIES OF FROZEN CELLS CATEGORIZED

BY SEROLOGICAL HL-A TYPES

HL-A Type	# Tested
1,8	26
2,12	18
3,7	13
2,7	5
29,12	5
2,40	5
2,27	3
2,5	4
11,35	2
2,17	3
2,15	2
2,8	2
32,8	1
28,12	1
1,17	1
28,35	1
24,35	1
3,14	1
2,60	1
9,12	1
1,35	1
Total:	97

INVENTORY OF FROZEN CELLS WITH SEROLOGICAL TYPE:

HL-A A1,B8

Identification Number	Total # Vials
139	58
110	124
120	86
106	189
158	272
17	129
03	134
99	82
69	59
147	49
10	149
144	20
09	119
146	59
13	47
70	67
05	112
16	14
180	98
129	29
90	58
213	95
214	80
29	410
28	416
A	30

HL-A, A2, B8

93	142
24	52

HL-A A32, B8

A2	166

Inventory of Frozen Cells with Serological Type:

HL-A A2, B12

Identification Number	Total # Vials
161	71
212	50
183	73
221	185
190	99
206	122
141	39
143	38
111	87
198	98
53	54
133	100
94	120
97	45
91	394
86	79
105	76
22	118
HL-A A29, B12	
09	40
155	62
104	96
40	50
27	255
HL-A A9, B12	
201	487

INVENTORY OF FROZEN CELLS WITH SEROLOGICAL TYPE:

HL-A A3, B7

Identification Number	Total # Vials
76	9
75	40
07	50
116	119
134	117
135	100
130	100
08	21
119	67
02	745
04	48
216	10
117	139

HL-A A2, B7

01	190
140	179
121	81
92	61
85	138

HL-A A2, B27

162	91
153	94
150	77

INVENTORY OF FROZEN CELLS WITH SEROLOGICAL TYPE:

Identification Number		Total # Vials
	HL-A A2,B40	
151		25
157		94
154		90
172		98
149		134
	HL-A A11,B35	
148		145
30		797
	HL-A A2,B17	
42		38
43		247
41		28
	HL-A A2, B15	
177		230
15		1033
	HL-A A2,B5	
159		146
14		79
36		17
24		71
	HL-A A1,B17	
145		52
	HL-A A24,B35	
152		59
	HL-A A1,B35	
195		90
	HL-A A28, B35	
228		117
	HL-A A2, B60	
64		79
	HL-A A3,B14	
B6		42

INVENTORY OF FROZEN CELLS WITH HETEROZYGOUS HL-A TYPE FOR RANDOM PANEL

Identification Number	HL-A Type	Total # Vials
18	1,28	130
20	2,11,12,22	275
25	2,24,35,38	194
31	2,29,15	99
35	2,11,5,35	63
37	10,30,35,18	69
39	11,28,8,22	59
44	26,33,12,38	126
45	3,29,12,21	66
47	3,24,7,40	53
48	2,26,16,27	308
49	26,23,35,37	75
50	2,26,16,17	93
51	2,9,12,27	54
52	1,26,8,38	139
61	2,32,7,12	72
62	1,2,40	40
65	3,31,5,7	54
66	25,26,7,18	54
68	30,31,13,21	45
70	1,2,8,40	134
71	2,24,12,35	61
72	1,11,8,13	54
73	24,33,17,35	40
78	1,36,17	67
83	29,30,7,12	65
84	1,30,7,8	73
96	1,25,8,17	151
101	2,26,17	120
122	2,31,8,15	60
123	2,32,12,18	65
124	3,19,12,35	104
125	2,5,27	143
126	3,18,15	57
127	1,2,7,8	45
128	1,2,5,15	104
131	1,2,12	33
132	25,29,12,18	130
136	3,33,17	39
137	2,29,12,17	93
138	2,3,5,7	147
142	2,3,8,12	34
165	3,28,12,17	49
167	9,31,33,17	99
168	3,28,12	124
189	1,11,17	118
191	1,28,35,8	32
202	3,31,40	459
210	1,2,17,35	143
221	29,24,7	128

Total: 50

SUMMARY OF HL-A D TYPING PERFORMED ON PARTIAL PANEL OF FROZEN CELLS

L.D. #	HL-A A	HL-A B	DW 1	DW 2	DW 3	DW 4	DW 5	DW 6	DW 107	DW 108
14	2	5								
31	2,29	15								
48	10	4,27								
52	1,10	8,N								
35	2,11	5,35								
02	3	7								
181	2,3	7,40								
61	2,32	7,12								
123	2,10	12,18								
03	1	8								
127	1,19	8,14								
96	1,10	8,7								
84	1,11	7,8								
122	2,11	8,15								
83	29,30	7,12								
73	9,33	17,35								
15	2	15								
91	2	12								
209	2,9	12,15								
20	2,11	12,22								
125	2	5,27								
70	1,2	8,40								
175	1,10	7,40								
51	2,9	12,27								
71	2,9	12,22								
101	2,10	17								
35	2,10	4,35								
39	11,28	8,22								
44	10,26	12,16								
26	28	12								
174	3,9	7,12								
49	9,10	37								
62	1,2	40								
128	1,2	5,15								
208	3	5								
45	3,29	12,21								
56	1,2	14,14								
124	3,29	12,35								

Statistical Analysis

The following is a typical statistical analysis of an experiment where a panel of responding cells (1st column) was tested in mixed lymphocyte culture against an HL-A D typed panel (top row) in order to determine the HL-A D types of the responding cells.

The cell combinations are cultured for six days. Tritiated thymidine, added to the cultures during the last 18 hrs, is incorporated into the DNA of dividing cells. Numbers represent median counts per minute, reflecting the degree of similarity between the responding and stimulating cells, as greater similarity results in less stimulation of cellular proliferation.

DOUBLE NORMALIZED VALUES

	CONTROL	568/7	569/5	520/	521/	522/5	545/	562/6	563/	537/17
RESPONDER (1)	195	124	274	175	142	74	295	-99	127	71
RESPONDER (3)	815	76	4	54	25	28	69	56	59	105
RESPONDER (4)	34	23	81	63	102	43	100	100	117	21
RESPONDER (5)	1609	36	6	76	33	7	102	45	37	84
RESPONDER (6)	1145	44	106	64	147	101	66	1	84	72
RESPONDER (7)	148	102	150	92	94	69	100	60	83	78
RESPONDER (8)	143	76	51	132	98	85	101	157	81	145
RESPONDER (9)	531	121	8	108	46	48	82	152	68	100
RESPONDER (10)	496	45	87	76	116	119	60	82	109	40
RESPONDER (11)	525	32	97	52	81	106	96	1	110	41
RESPONDER (12)	108	43	62	87	91	109	77	112	7	81
RESPONDER (13)	1846	68	26	-99	75	88	62	34	64	128
RESPONDER (14)	682	117	83	-99	14	95	92	38	87	79
RESPONDER (15)	592	98	103	-99	69	99	92	12	91	46
RESPONDER (16)	92	28	33	-99	80	87	59	8	85	100

DOUBLE NORMALIZED VALUES

	540/8	539/5	531/5	552/4	554/	555/	553/5	526/6	524/4
RESPONDER (1)	122	107	269	95	73	76	102	17	-99
RESPONDER (3)	103	99	49	120	37	55	33	16	107
RESPONDER (4)	30	16	100	86	86	95	70	37	13
RESPONDER (5)	40	32	41	124	40	19	12	5	15
RESPONDER (6)	128	167	103	97	114	140	114	229	1
RESPONDER (7)	77	96	95	66	73	71	92	16	29
RESPONDER (8)	133	120	53	103	106	111	75	163	136
RESPONDER (9)	97	71	37	106	100	57	32	-99	156
RESPONDER (10)	77	83	71	65	80	75	115	-99	16
RESPONDER (11)	62	79	92	42	107	113	98	-99	-99
RESPONDER (12)	66	101	-99	48	100	105	122	-99	19
RESPONDER (13)	81	50	-99	66	77	80	71	-99	73
RESPONDER (14)	72	24	-99	71	71	33	41	-99	18
RESPONDER (15)	44	28	-99	37	28	32	64	-99	44
RESPONDER (16)	35	66	-99	76	69	72	92	-99	93

DOUBLE NORMALIZED VALUES

	529/	559/6	561/	503/1	564/	565/3	566/17	567/	534/1	535/17
RESPONDER (1)	-99	14	1	2	3	1	1	-99	-99	-99
RESPONDER (3)	116	19	74	88	109	97	100	97	143	73
RESPONDER (4)	48	97	115	72	96	28	21	32	6	7
RESPONDER (5)	22	9	78	51	97	44	100	27	35	62
RESPONDER (6)	76	146	116	101	71	87	59	303	36	36
RESPONDER (7)	68	82	74	85	103	70	85	83	100	80
RESPONDER (8)	117	213	104	28	25	118	113	149	110	115
RESPONDER (9)	109	27	88	153	110	103	87	20	114	100
RESPONDER (10)	8	84	110	40	73	34	55	100	3	36
RESPONDER (11)	29	141	85	89	86	28	51	82	5	47
RESPONDER (12)	100	86	72	109	68	14	86	119	72	64
RESPONDER (13)	62	15	68	100	79	56	101	39	61	101
RESPONDER (14)	13	103	83	78	70	126	98	34	61	56
RESPONDER (15)	30	58	96	96	83	109	79	54	33	45
RESPONDER (16)	29	13	90	100	105	77	101	92	66	110

DOUBLE NORMALIZED VALUES

	533/1	532/	530/4	541/1	542/1	544/	557/1	548/	546/2	547/
RESPONDER (1)	-99	-99	-99	-99	1	-99	-99	-99	-99	-99
RESPONDER (3)	102	116	100	116	131	66	157	94	85	104
RESPONDER (4)	19	62	67	62	14	74	18	73	58	100
RESPONDER (5)	50	97	67	53	72	89	34	101	80	81
RESPONDER (6)	73	96	99	100	37	79	39	89	134	79
RESPONDER (7)	94	68	59	66	104	84	70	67	2	72
RESPONDER (8)	100	96	111	43	135	117	141	99	101	166
RESPONDER (9)	-99	115	73	87	106	100	136	99	100	88
RESPONDER (10)	-99	87	68	101	5	82	4	81	85	75
RESPONDER (11)	-99	62	135	74	65	66	39	92	125	82
RESPONDER (12)	-99	38	130	76	96	66	56	126	84	76
RESPONDER (13)	-99	123	79	49	75	59	91	77	99	81
RESPONDER (14)	-99	89	56	109	86	87	100	100	49	94
RESPONDER (15)	-99	100	56	47	45	100	89	145	9	95
RESPONDER (16)	-99	92	61	73	73	105	94	96	44	129

DOUBLE NORMALIZED VALUES

	549/	543/	523/5	558/	30/1	14/1	020/2	01/2	29/3	03/3
RESPONDER (1)	-99	-99	-99	-99	-99	-99	-99	-99	-99	-99
RESPONDER (3)	101	91	19	84	103	103	74	100	97	86
RESPONDER (4)	61	48	77	24	83	100	45	83	20	3
RESPONDER (5)	70	56	11	48	133	94	60	118	124	87
RESPONDER (6)	55	83	111	50	97	75	119	94	85	74
RESPONDER (7)	74	80	99	67	86	77	2	17	70	66
RESPONDER (8)	100	116	78	146	42	28	117	97	117	100
RESPONDER (9)	89	110	39	116	111	90	102	83	97	100
RESPONDER (10)	22	82	102	39	90	65	48	83	70	62
RESPONDER (11)	39	125	88	77	65	96	83	116	32	2
RESPONDER (12)	117	95	100	68	83	63	100	76	38	13
RESPONDER (13)	86	83	102	100	100	85	80	102	100	94
RESPONDER (14)	109	100	68	53	77	78	48	82	66	100
RESPONDER (15)	80	85	86	61	72	104	5	32	48	131
RESPONDER (16)	72	53	79	101	69	117	6	52	112	96

DOUBLE NORMALIZED VALUES

	91/4	22/4	DBH/6	53/	40/	151/	157/	154/	172/	149/
RESPONDER (1)	-99	-99	-99	-99	-99	-99	-99	-99	-99	-99
RESPONDER (3)	102	99	31	85	45	95	71	96	92	443
RESPONDER (4)	52	80	52	88	61	87	73	102	44	13
RESPONDER (5)	46	94	86	115	81	117	115	81	54	12
RESPONDER (6)	116	93	141	56	50	80	61	104	143	81
RESPONDER (7)	53	97	50	99	92	108	104	100	100	11
RESPONDER (8)	100	110	129	26	124	106	100	86	159	100
RESPONDER (9)	101	98	100	99	71	78	59	84	45	285
RESPONDER (10)	75	116	87	100	57	88	77	63	38	13
RESPONDER (11)	61	87	90	68	45	67	73	88	110	17
RESPONDER (12)	75	76	130	71	67	65	91	103	40	19
RESPONDER (13)	98	100	41	82	100	76	70	94	49	135
RESPONDER (14)	78	127	55	77	47	67	92	73	30	7
RESPONDER (15)	29	96	10	124	124	100	105	55	39	24
RESPONDER (16)	95	92	13	106	106	85	97	81	76	28

DOUBLE NORMALIZED VALUES

	153B/	162/	150/	POOL	530/4	550/
RESPONDER (1)	-99	-99	1	-99	-99	-99
RESPONDER (3)	84	100	123	79	104	56
RESPONDER (4)	33	38	52	93	88	50
RESPONDER (5)	35	29	88	90	84	73
RESPONDER (6)	113	270	100	100	96	-99
RESPONDER (7)	59	50	74	117	-99	83
RESPONDER (8)	100	112	-99	108	-99	97
RESPONDER (9)	107	151	-99	78	-99	103
RESPONDER (10)	97	34	-99	92	-99	61
RESPONDER (11)	86	50	-99	61	-99	-99
RESPONDER (12)	135	67	-99	80	-99	5
RESPONDER (13)	85	31	-99	77	-99	59
RESPONDER (14)	70	38	-99	96	-99	112
RESPONDER (15)	55	2	-99	136	-99	130
RESPONDER (16)	28	1	-99	92	-99	65

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18. SUPPLEMENTARY NOTES

19. KEY WORDS *(Continue on reverse side if necessary and identify by block number)*

LD Typing, Bone Marrow Transplantation, Homozygous Cells, HLA-D, Human Histocompatibility, Mixed Lymphocyte Culture

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

The primary goal of this work was to identify homozygous typing cells which could be used in various test systems to identify the tissue typing antigens of the fourth locus of the human histocompatibility system. The following has been accom-→

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plished: 1)serological testing for HLA_A,B and C loci revealed a population that appeared to be homozygous for these determinants. Several of these persons' cells have also been shown to be homozygous for HLA-D. 2)Mixed lymphocyte cultures (MLC) were undertaken between these individuals and members of our HLA-D typed panel. 3) Lymphocyte cultures with a panel of known homozygous typing cells enabled the authors to assign specificities to several of the cells collected. Some unexpected reactions may provide information for the identification of new specificities. 4) A panel of over 60 cells have been typed for all known HLA--A,B and C antigens as well as with homozygous cells to establish D specificities.

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